



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07C 251/58, C07D 295/08 C07C 295/12, 249/12 A61K 31/15		A1	(11) International Publication Number: WO 90/04584 (43) International Publication Date: 3 May 1990 (03.05.90)
<p>(21) International Application Number: PCT/HU89/00048</p> <p>(22) International Filing Date: 19 October 1989 (19.10.89)</p> <p>(30) Priority data: 5405/88 20 October 1988 (20.10.88) HU</p> <p>(71) Applicant (<i>for all designated States except US</i>): BIOREX KUTATÓ FEJLESZTŐ KFT. [HU/HU]; Medve u. 25-29, H-1027 Budapest (HU).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): LITERÁTI NAGY, Péter [HU/HU]; VIL u. 38, H-1172 Budapest (HU). BALÁZS, Béla [HU/HU]; Kaptárkó u. 2, H-1118 Budapest (HU). BOROSS, Mária [HU/HU]; Pauler u. 4, H-1013 Budapest (HU). SZILBÉREKY, Jenő [HU/HU]; Szamos u. 7, H-1122 Budapest (HU). ZSILÁGA, Gizella [HU/HU]; Jász u. 94, H-1131 Budapest (HU). ABRAHÁM, Lajos [HU/HU]; Vécsei u. 4, H-1054 Budapest (HU). BLASKÓ, György [HU/HU]; Zöldlomb u. 32, H-1025 Budapest (HU). GACHÁLYI, Béla [HU/HU];</p>			
<p>Damjanich u. 26, H-1071 Budapest (HU). ALMÁSI, Attila [HU/HU]; Izabella u. 48, H-1064 Budapest (HU). NÉMETH, Gábor [HU/HU]; Zsókavár út 48, H-1157 Budapest (HU).</p> <p>(74) Agent: S.B.G. & K.; Dalszinház u. 10, H-1061 Budapest VI (HU).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), SU, US.</p> <p>Published <i>With international search report.</i></p>			
<p>(54) Title: NOVEL O-(3-AMINO-2-HYDROXYPROPYL)-HYDROXIMIC ACID HALIDES AND PROCESS FOR PREPARING THE SAME</p> <p>(57) Abstract</p> <p>The present invention relates to novel hydroximic acid halides, the preparation of the same, pharmaceutical compositions containing the above novel compounds as active ingredients as well as the use of the said compounds in the therapy of diabetic angiopathy. The novel hydroximic acid derivatives are illustrated by the general formula (I), wherein X is halo, such as fluoro, chloro, bromo and iodo; R¹ is hydrogen or C₁₋₅alkyl; R² is C₁₋₅alkyl, C₅₋₇cycloalkyl or phenyl optionally substituted with hydroxy, or R¹ and R², when taken together with the adjacent nitrogen, form a 5 to 8 membered ring optionally containing additional nitrogen and/or oxygen atom, which ring may also be condensed with a benzene ring; R³ is hydrogen, phenyl, naphthyl or piridyl optionally substituted with one or more halo or alkoxy; R⁴ is hydrogen or phenyl; R⁵ is hydrogen or phenyl; m is 0, 1 or 2 and n is 0, 1 or 2.</p>			

AP

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MR	Mauritania
BE	Belgium	GA	Gabon	MW	Malawi
BF	Burkina Faso	GB	United Kingdom	NL	Netherlands
BG	Bulgaria	HU	Hungary	NO	Norway
BJ	Benin	IT	Italy	RO	Romania
BR	Brazil	JP	Japan	SD	Sudan
CA	Canada	KP	Democratic People's Republic of Korea	SE	Sweden
CF	Central African Republic	KR	Republic of Korea	SN	Senegal
CG	Congo	LI	Liechtenstein	SU	Soviet Union
CH	Switzerland	LK	Sri Lanka	TD	Chad
CM	Cameroon	LU	Luxembourg	TG	Togo
DE	Germany, Federal Republic of	MC	Monaco	US	United States of America
DK	Denmark				

-1-

Novel O-(3-amino-2-hydroxypropyl)-hydroximic acid halides and process for preparing the same.

Technical field

The present invention relates to novel hydroximic acid halides, the preparation of the same, pharmaceutical compositions containing the above novel compounds as active ingredient as well as the use of the said compounds in the therapy of diabetic angiopathy.

Background art

One of the most frequent metabolism diseases is diabetes mellitus, the main symptom of which is the disturbance of the balance of carbohydrate metabolism in the organism. Diabetes mellitus is often accompanied by pathological vascular deformations, e.g. vasoconstrictions in the limbs, pathological deformation of the eyeground vessels, etc. Though, in addition to insulin a large number of effective drugs are known, in the field of the treatment of diabetic angiopathy associated with the basic disease, results provided by the commercially available compositions are quite poor. This situation is caused by the phenomenon that diabetes mellitus results in changes of the vascular adrenerg receptors, and consequently, medical treatment with the commercially available drugs results in adrenerg reaction different from those taking place in the blood vessels of non-diabetic patients. (Nature

-2-

- New Biology, 243, No. 130, 276 /1973/; Szemészet, 111, 23 /1974/; Endocrinology, 93, 752 /1973/). The adrenerg receptors of blood vessels in diabetic patients undergo a transformation into beta receptors due to the quantitative increase of the metabolism. For the receptor transformation, the release of a modulator is responsible (Amer.J.Physiol., 218, 869 /1970/). After addition of the modulator to the alpha organ the alpha agonists will not be active any more as the receptor is transformed into beta.
- 10 The original alpha sensibility may be recovered by adding a special beta blocking agent into the organism.

In case of qualitative alteration of the metabolism in model or human in vivo diabetes the alpha agonists, e.g. noradrenalin, remain effective, this effect, however, may be compensated by the addition of beta blocking agents. This is the first functional change which is detectable in diabetes, e.g. by addition of Alloxane (Hexahydropirimidin-tetraon), 24 hours after the administration. In case of diabetes an imperfect alpha-beta receptor transformation - possibly due to the formation of an alternative, so-called "Falsch" modulator - serves as starting point of the pathological changes.

Disclosure of the invention

It has been found that the novel compounds of the formula (I) wherein

25 X is halo, such as fluoro, chloro, bromo and iodo.
R¹ is hydrogen or C₁₋₈ alkyl,

- 3 -

R² is C₁₋₅ alkyl, C₅-> cycloalkyl or phenyl each optionally being substituted with hydroxy, and

R¹ and R², when taken together with the adjacent nitrogen atom, form a 5-8 membered ring optionally containing additional nitrogen and/or oxygen atom, which ring may also be condensed with a benzene ring, R³ is hydrogen, phenyl, naphtyl or piridyl optionally substituted with one or more halo or alkoxy,

R⁴ is hydrogen or phenyl,

10 R⁵ is hydrogen or phenyl,

m is the integer of 0, 1 or 2 and

n is the integer of 0, 1 or 2,

essentially do not influence, or only slightly, the adrenerg reactions of the healthy blood vessels, but show a strong

15 effect on the adrenerg receptors deformed by the diabetes mellitus. This effect appears in the first line as a selective beta-blocking effect, consequently, the compounds of the general formula (I) are useful in medical influencing of diabetic angiopathy.

20 The common beta-blocking agents <Inderal, 1-(methyl-ethyl-amino)-3-(1-naphtalenyloxy)-2-propanol, Visken, 4,5-dihydro-2-(5-methyl-2-/1-methyl-ethyl-phenoxy/-methyl)-1H-imidazol> are contraindicated in the therapy of diabetic angiopathy.

25 Diabetes selective adrenerg receptor blocking compounds are described in Hungarian Patent No. 177,578, "Process for preparing novel OF-(3-amino-2-hydroxypropyl)-amidoxim derivatives".

All other object of the invention is the process for prepar-

- 4 -

ing the compounds of the general formula (I) and the salts thereof. According to the process

- a) an aldoxim of the general formula (III) wherein R³, R⁴, R⁵, m and n are as defined above, is reacted in the presence 5 of a base with an amine of the general formula (IV/A) and (IV/B), resp., wherein R¹ and R² are as defined above and X is halo, or
- b) an aldoxim of the general formula (III), wherein R¹, R², R³, m and n are as specified above, is reacted with epichlorohydrine and the aldoxim derivative of the general formula 10 (VI) thus obtained is reacted with an amine of the general formula (V), wherein R¹ and R² are as specified above, to obtain the aldoxim derivatives of the general formula (VII), and
- 15 the compounds of the general formula (VII) according to the above processes a) or b) are reacted with inorganic acid halides, or other halogenating agents, e.g. POX₃, SOX₃, PX₃ - wherein X is halo - to obtain the halo derivatives of the general formula (VIII), and by replacing the halo atom on the 20 aliphatic chain thereof with hydroxy, the compounds of the general formula (I) are obtained, or
- c) an amidoxim derivative of the general formula (II) is diazotized in the presence of NaNO₂ and HX - wherein X is halo - and subjected to "boiling away" reaction.
- 25 If desired, the free bases of the general formula (I) may be transformed to acid addition salts by reacting with organic or inorganic acids, or the compounds obtained as salts may be transformed into the free bases.

SUBSTITUTE SHEET

- 5 -

According to a preferred embodiment of the process a) the reaction is carried out in aqueous medium, in an aqueous organic solvent, such as aqueous alcohol or in organic solvents, preferably at a temperature of 0 to 140°C.

5 According to an other embodiment of the process variant a) the salts of the aldoximes of the general formula (III) are formed in dry alcoholic medium with alkali alcoholates, and subsequently the solutions of the amines of the general formulae (IV/A) and (IV/B), resp., in alcohol are added
10 thereto. The reaction is preferably carried out at a temperature of 0 to 100°C under stirring.

According to a still another embodiment of the process variant a) the salts of the aldoximes of the general formula (III) are formed in a solvent non-miscible with water, such 15 as benzene, toluene, xylene, with alkali hydroxides, preferably sodium or potassium hydroxide. The salt forming is carried out at the boiling temperature of the solvent, and the water forming during the reaction is continuously removed by azeotropic distillation, followed by the addition of the
20 solution of the compounds of the general formulae (IV/A) and (IV/B), resp.

According to an other embodiment of the process variant a) the reaction is carried out in aqueous medium, by adding to the compounds (IV/A) or (IV/B) the aqueous-alkaline solution
25 or suspension of the aldoximes under stirring.

The reaction is carried out preferably at a temperature of 0 to 60°C and the aldoxim is added to the reaction mixture in

SUBSTITUTE SHEET

- 6 -

the form of a solution or suspension of a temperature of 5 to 20°C in aqueous alkali solution. The reaction may also be carried out in a mixture of water and an organic solvent, wherein to the solution of the compound of the 5 general formula (IV/A) or (IV/B) in alcohol or dioxane the aqueous-alkaline solution or suspension of the aldoxim is added dropwise. The addition may also be accomplished in reversed order, i.e to the aqueous-alkaline solution or suspension of the aldoxim is added the other reaction partner.

10 According to process variant b) the aldoxim of the general formula (III) is reacted with epichlorohydrine in the presence of a base. If desired, the epoxy compound obtained during the reaction may be isolated, it is preferred, however, to carry out the reaction in one synthesis step, without 15 isolating the intermediate, in aqueous medium or in an organic solvent, aqueous organic solvent, or in a two-phase system, at a temperature of -10 to + 60°C, by adding the reagent in one or two portions or dropwise. The order of addition may be reversed, i.e. either the alkaline solution or suspension 20 of the aldoxim is added to the epichlorohydrine, or the aldoxim is added to the mixture of the epichlorohydrine and base. If desired, the intermediate of the formula (VI) may be separated by extracting with a solvent non-miscible with water. It is more preferred, however, to react the compound 25 of the general formula (VI) without isolation with the corresponding amine.

The process variant b) may also be carried out in dry sol-

SUBSTITUTE SHEET

- 7 -

vents, preferably dry alcohols. In this case the alkali metal salt of the aldoxim is formed, suitably by dissolving the aldoxim in a solution of alkali alcoholate in alcohol. Following the addition of the epichlorohydrine, the reaction mixture is allowed to stand for 1 to 5 days at a temperature of 0 to 20°C and subsequently the reaction is carried on by the addition of the corresponding amine, at ambient temperature or by heating the mixture. Besides the alcohol, as dry solvent also other organic solvents, e.g. aceton, dimethyl sulfoxide, dimethyl formamide, etc. or the mixtures thereof may be used.

The compounds of the general formula (VII) obtained according to the processes a) or b) can be isolated by methods known per se. If aqueous medium is used, the isolation is generally accomplished by extraction, followed by drying and evaporating the solvent. Subsequently the aldoxim derivative of the formula (VII) is boiled with the inorganic acid halides, such as PCl_5 , SOCl_2 , POCl_3 for 1 to 5 hours in the presence or absence of a solvent, preferably halogenated solvents, such as CHCl_3 . The compounds of the general formula (VII) thus obtained can be isolated by making the mixture alkaline with aqueous alkali, followed by extraction.

The compound of the general formula (VIII) is a hydroximic acid halogenated in the chain. It has been found that the halo moiety thereof will not enter into nucleophytic substitution reaction under the reaction conditions, and accordingly, the formation of the OH group will be accomplished selec-

- 8 -

tively, in one step by aqueous-alkaline hydrolysis at a temperature of 0 to 100°C, using preferably alkali hydroxides or other metal hydroxides, e.g. silver hydroxide, or in two steps, first forming an ester moiety suitably with the alkali 5 salts of lower carboxylic acids followed by the hydrolysis to obtain the compounds of the general formula (I).

The reaction conditions of process variant c) are selected so that the temperature is maintained between -5 and +10°C and thus, also the "boiling away" reaction takes place.

- 10 Preferably the reaction is carried out in water, and the intermediate diazonium salt is not isolated but also the "boiling away" reaction is carried out by selecting suitable reaction conditions thus obtaining the compounds of the general formula (I).
- 15 The reaction products can be separated from the reaction mixture by methods known per se, e.g by crystallisation and extraction, when using water as reaction medium. When organic solvents are used, crystallisation or evaporation followed by washing with water and extraction is applied. The products 20 may be isolated in the form of salts thereof, or from the isolated bases salts may be formed by using molar equivalent of mineral or organic acids, preferably pharmaceutically acceptable acids, or, if desired, from the salts the free bases can be obtained.

- 25 The general beta-blocking effect of the compounds of the general formula (I) was studied on anaesthetised cats. In these tests besides registering the blood pressure and pulse

- 9 -

rate, also the effect of the test materials on the left ventricular contractility was studied. As reference material Inderal <1-isopropylamino-3-(naphtyloxy)-propan-2-ol> was used.

5 The beta-blocking effect of the compounds according to the present invention was tested on rat aorta spiral and/or ring preparate <J.Pharmacol.Exp.Therap. 158, 531 (1967)>. The experimental diabetes was induced with Streptosotocin <2-(3-nitroso-3-methylureido)-2-deoxy-D-glucose>. The reaction was evaluated as positive when the alpha stimulating effect of the noradrenalin on the control preparate, i.e. that having not been treated with Streptosotocin, was not influenced, but protected on the diabetic aorta. In the tests carried out with the compounds according to the present 10 invention a general selective effect occurred, manifesting in case of diabetic tests in a strong, in case of normal tests in the absence of or in the presence of only a slight beta-blocking effect.

Experiments were carried out to study whether on the aorta 20 spiral preparates of diabetic animals treated with Streptosotocin the Inderal protects the contractions induced by noradrenalin. As control, animals previously not treated with Streptosotocin were used. The results obtained essentially conformed to those known from the literature <Amer.J.Physiol., 218, 869 (1970)>, i.e. the alpha stimulating effect of noradrenalin was protected by the Inderal in diabetic tests, but not in the normal tests. (Endocrinology, Vol. 93, No.

- 10 -

3, Sept. 1973).

It has been found that the compounds of the general formula (I) showed a slight general beta-blocking effect. Compared with the control beta-blocking Inderal the compound tested showed an effect of two orders of magnitude less in the inhibition of the beta-blocking D,L-1-(3,4-dihydroxy-phenyl)-2-isopropylamino-ethanol.

At the same time the compounds of the general formula (I) produced a significant parallel shift to the right of the noradrenalin dose-response curve in diabetic rat aorta ring (and/or spiral) in the order of magnitude of the effect of Inderal. The dose of Inderal was 0,5 micrograms/ml, while the dose of the compounds of the general formula (I) was 1,0 microgram/ml.

Accordingly, the O-(3-amino-2-hydroxypropyl)-hydroximic acid halides of the general formula (I) may preferably be used in the therapy of any kind of diabetic micro- and macroangiopathy, especially of diabetic retinopathy and diabetic nephropathy in case of diabetes mellitus. The above compounds can be used per se or in the form of pharmaceutical preparations.

The above treatment and pharmaceutical compositions also form the object of the present application. The pharmaceutical compositions of the present invention can be used for prevention, for treatment in the active phase of the disease as well as in acute cases.

The hydroximic acid halides of the general formula (I) are effective exclusively on patients in the stadium of formation

- 11 -

of diabetes, and are ineffective on non-diabetic persons.

Best mode of carrying out the invention

Preferred are those compounds of the general formula (I) wherein X is chloro, m and n are each 0, R³ is 3,4-
5 dimethoxybenzyl, piridyl, napthyl or indolyl and R¹ is and R² is isopropyl, 2-hydroxyethyl or t-butyl, or R¹ and R² together form pentamethylene. Especially preferred active compounds are those mentioned in the following examples.

The invention is further illustrated in the following examples. It is to be understood, however, that the scope of protection is not limited to the matter disclosed in the examples any way.

Example 1.

2,3 g of sodium were dissolved in 200 ml of abs. ethanol and
15 then 12,1 g of benzaldoxim were added. At boiling temperature the solution of 3-piperidino-2-hydroxy-1-chloropropane prepared from 9,3 g epichlorohydrine and 8,5 g of piperidine in 50 ml of abs. ethanol by methods known per se was added dropwise. The reaction mixture was boiled for 8 hours under
20 reflux, the precipitated salt was filtered at room temperature and the solvent was distilled off in vacuo. To the residue 100 ml of 5% sodium hydroxide were added and the oily product was extracted with benzene. After drying and evaporating the benzene extract 8,2 g of O-(3-piperidino-2-hy-

- 12 -

droxy-1-propyl)-benzaldoxim was obtained. The hydrochloride of the product was separated from the isopropanol solution thereof by introducing gaseous hydrochloric acid into or adding hydrochloric acid in ethanol to the solution. Mp.

5 137°C (from isopropanol).

Analysis based on $C_{15}H_{22}ClN_2O_2$: Mw. 298,81

Calculated: C 60,29, H 7,76, N 9,37, Cl 11,86;

Found: C 60,35, H 8,00, N 9,25, Cl 11,90%.

2,98 g of O-(3-piperidino-2-hydroxy-1-propyl)-benzaldoxim
10 were boiled in 20 ml of thionyl chloride for 3 hours. The O-(3-piperidino-2-chloro-1-propyl)-benzhydroximic acid chloride was separated by adding about 100 ml of 20 % aqueous base until pH = 11 followed by extraction with chloroform. The chloroform extract was dried over sodium sulfate and evaporated.
15 The oil-like product can be transformed into the compound of the general formula by different ways:

a) 3,4 g of oily product were hydrolyzed with 20 ml of 20% NaOH at 55 to 60°C for 2 hours under stirring, extracted with benzene, the benzene solution was dried with solid drying agent and subsequently evaporated. To the residue 50 ml of hydrochloric acid in ethyl acetate was added. Under stirring the hydrochloride of the O-(3-piperidino-2-hydroxy-1-propyl)-benzhydroximic acid chloride precipitated.

Yield: 2,1 g. NMR (base, $CDCl_3$): 7,4-8,0 m (5H); 3,9-4,4 m (3H); 2,2-2,8 m (6H); 1,3-1,8 m (6H); 3,5 s (OH).
25

Mp. 140-142°C (from isopropanol)

Analysis: based on $C_{15}H_{22}Cl_2N_2O_2$:

- 13 -

Calculated: C 54,22, H 6,37, N 8,43, Cl 21,14;

Found: C 53,12, H 6,26, N 8,19, Cl 20,84%.

b) 0,81 g (4,74 mmoles) of AgNO₃ were dissolved in 4 ml of water and under stirring 0,19 g of NaOH (4,74 mmoles) in 3 ml of water was added thereto dropwise. The aqueous suspension of the AgOH precipitate was stirred with 1,5 g (4,74 mmoles) of O-(3-piperidino-2-chloro-1-propyl)-benzhydroximic acid chloride at 50°C for 3 hours. Then the suspension was extracted with benzene, the benzene layer was dried with sodium sulfate, filtered, evaporated and subjected to the salt forming step described in process a). Yield 95%. The physical data of the end product are identical with those in process a).

c) 3,0 g (9,49 mmoles) of
15 O-(3-piperidino-2-chloro-1-propyl)-benzhydroximic acid chloride were dissolved in 10 ml of ethanol, under stirring 0,86 g (1,05.10⁻² moles) of sodium acetate in 15 ml of water were added and the mixture was stirred for 3 hours at 50°C. The reaction mixture was evaporated in vacuo and the residue was extracted with benzene. The benzene extract was dried over sodium sulfate and evaporated, thus providing 2,12 g of oily O-(3-piperidino-2-acetoxy-1-propyl)-benzhydroximic acid chloride. The ester thus obtained was dissolved in 20 ml of ethanol followed by the addition of 20 ml of water. 0,25 g of
20 NaOH in 20 ml of water were added to the mixture and stirred at 40°C for one hour, extracted with benzene, the benzene extract was dried with sodium sulfate and evaporated. From
25

- 14 -

the residue salt was formed according to the method in process a). Yield 90%. The quality of the product was identical with that of process a).

Example 2.

5 Following the process as described in Example 1 but starting from 3-piridyl-aldoxim and 3-piperidino-2-hydroxy-1-chloro-propane the O-(3-piperidino-2-hydroxy-1-propyl)-3-piridyl-aldoxim was prepared, which was reacted with thionyl chloride according to Example 1. After removing the thionyl chloride 10 by evaporation, isopropanol was added to the residue thus crystallising the O-(3-piperidino-2-chloro-1-propyl)-3-piridyl-hydroximic acid chloride in the form of the dihydrochloride. Mp. 142°C (from isopropanol). Yield 85 %.

Analysis based on $C_{14}H_{21}Cl_4N_3O$: Mw = 389,15

15 Calculated: C 43,21, H 5,44, N 10,79, Cl 36,44;
Found: C 42,97, H 5,62, N 10,59, Cl 36,80%.

According to another mode of preparation the O-(3-piperidino-2-chloro-1-propyl)-3-piridyl-hydroximic acid chloride dihydrochloride obtained as above was not isolated, instead, to the evaporation residue 10 % NaOH was added until a pH of 11 in accordance with Example 1 and the mixture thus obtained was extracted with chloroform. The chloroform layer was dried, evaporated and subsequently hydrolyzed by using any of the processes a), b) and c) of Example 1. The hydrolysis mixture was extracted with benzene, dried with sodium sulfate and evaporated. The residue was dissolved in acetone

- 15 -

followed by the addition of maleic acid and isolating the O-(3-piperidino-2-hydroxy-1-propyl)-3-pyridyl-hydroximic acid chloride maleate thus obtained by filtering.

NMR (base, CDCl₃): 9,03, 8,59, 8,00, 7,1-7,4, 3,84 s (3H),
5 1,1-1,8 (6H), 5,28 s (OH).

Mp. 125°C (from aceton). Yield 65 %.

Analysis based on C₁₈H₂₄C1N₃O₆: Mw. = 413,79

Calculated: C 52,24, H 5,84, N 10,15, Cl 8,55;

Found: C 52,26, H 5,99, N 9,87, Cl 8,46%.

10 Example 3

To 3,5 g (10 mmoles) of O-(3-piperidino-2-hydroxy-1-propyl)-benzamidoxim dihydrochloride 40 mmoles of hydrogen chloride (in 37 % form) was added at 5°C under vigorous stirring.

After the addition of 5 ml of dioxane the mixture was cooled
15 to 0°C by using salt-ice. At the same temperature a solution
of 1,38 g (20 mmoles) of NaNO₂ in 6 ml water was added drop-
wise during a period of 1,5 hours followed by intensive
stirring for 4 hours at ambient temperature. The acidic
reaction mixture was made alkaline by the addition of 10 %
20 sodium hydroxide until a pH of 11 and then extracted with 80
to 100 ml of benzene. The benzene layer was dried over sodium
sulfate and evaporated. From the residue the hydrochloride of
the O-(3-piperidino-2-hydroxy-1-propyl)-benzhydroximic acid
chloride was formed by the addition of a saturated solution
25 of hydrochloric acid in ethyl acetate and isolated by filter-
ing. Mp. 139-141°C.

- 16 -

Analysis based on $C_{15}H_{22}Cl_2N_2O_2$: Mw = 333,25

Calculated: C 54,22, H 6,37, N 8,43, Cl 21,14;

Found: C 54,62, H 6,16, N 8,09, Cl 20,71%.

Example 4

5 The process described in Example 3 was followed but instead of hydrochloric acid, hydrogen bromide was used as hydrogen halide, thus obtaining the O-(3-piperidino-2-hydroxy-1-propyl)-benzhydroximic acid bromide hydrochloride. Yield 27 %.

Mp. 138°C (from isopropanol)

10 Analysis based on $C_{15}H_{22}BrClN_2O_2$: Mw = 377,71

Calculated: C 47,63, H 5,87, N 7,41;

Found: C 47,60, H 6,19, N 7,50%.

Example 5

Following the process as described in Example 3 O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic acid amidoxim dihydrochloride was diazotized, by using hydrochloric acid as hydrogen halide. Following the diazotizing and "boiling away" reaction from the O-(3-piperidino-2-hydroxy-propyl)-3-piperidyl-hydroximic acid chloride the maleate was formed in dry organic solvent by adding molar equivalent of maleic acid, and then separated. Mp. 125°C (from aceton). Yield 58 %.

Analysis based on $C_{15}H_{24}ClN_3O_6$: Mw = 413,79

Calculated: C 52,24, H 5,84, N 10,15, Cl 8,55;

Found: C 52,26, H 5,99, N 9,87, Cl 8,46%.

- 17 -

LD₅₀: 110 mg/kg iv. on Wistar rats.

Example 6

Following the process as described in Example 5 but using hydrogen bromide instead of the hydrochloric acid as hydrogen halide, the O-(3-piperidino-2-chloro-1-propyl)-3-pyridyl-hydroximic acid bromide maleate was obtained. Yield: 58 %.

Mp. 117°C (from aceton)

Analysis based on C₁₈H₂₄BrN₃O₆: Mw = 457,25

Calculated: C 47,36, H 5,21, N 9,16, Br 17,13;

10 Found: C 47,67, H 5,31, N 8,80, Br 16,78%.

Example 7

Following the process as described in Example 3 but using O-(3-piperidino-2-hydroxy-1-propyl)-3,3-diphenyl-propionic acid hydroximic acid dihydrochloride as amidoxim component in 15 the diazotizing reaction, the O-(3-piperidino-2-hydroxy-1-propyl)-3,3-diphenyl-propionic acid hydroximic acid dihydrochloride was obtained.

Yield: 30 %. Mp. 149-152°C (from isopropanol).

NMR (base, DMSO_d₆): 7,1-7,6 m (10H), 4,5 t (14), 3,34 d (2H),
20 J = 7,5 Hz, 3,9 br s (3H), 2,3-3,0 m (6H), 1,3-1,9 m (6H), OH shaded.

Analysis based on C₂₉H₃₆Cl₂N₂O₂2: Mw = 437,40

Calculated: C 63,15, H 6,51, N 6,40, Cl 16,21;

Found: C 63,50, H 6,79, N 6,31, Cl 16,47%.

- 18 -

Example 8

Following the process as described in Example 3 but using O-(3-diethylamino-2-hydroxy-1-propyl)-3,3-diphenyl-propionic acid amidoxim dihydrochloride as starting amidoxim component,
5 the O-(3-diethylamino-2-hydroxy-1-propyl)-3,3-diphenyl-propionic acid hydroximic acid chloride dihydrochloride was obtained. Yield: 32 %. Mp. 155°C (from isopropanol).
Analysis based on $C_{22}H_{30}Cl_2N_2O_2$: Mw = 425,40
Calculated: C 62,11, H 7,10, N 7,52, Cl 16,66;
10 Found: C 62,10, H 6,98, N 7,45, Cl 17,00%.

Example 9

Following the process as described in Example 3 but using O-(3-isopropylamino-2-hydroxy-1-propyl)-benzamidoxim dihydrochloride as starting amidoxim component, the O-(3-isopropylamino-2-hydroxy-1-propyl)-benzhydroximic acid hydrochloride was prepared. Yield 12 %. Mp. 122°C (from isopropanol).
Analysis based on $C_{13}H_{20}Cl_2N_2O_2$: Mw = 307,22
Calculated: C 50,82, H 6,56, N 9,11, Cl 23,08;
20 Found: C 51,12, H 6,58, N 9,05, Cl 22,89%.

- 19 -

Claims

1. Hydroximic acid derivatives of the general formula (I) and the salts thereof wherein

X is halo, such as fluoro, chloro, bromo and iodo,

5 R¹ is hydrogen or C₁₋₅ alkyl,

R² is C₁₋₅ alkyl, C₅₋₇ cycloalkyl or phenyl optionally substituted with hydroxy, or

R¹ and R², when taken together with the adjacent nitrogen, form a 5 to 8 membered ring optionally containing additional

10 nitrogen and/or oxygen atom, which ring may also be condensed with a benzene ring,

R³ is hydrogen, phenyl, naphtyl or piridyl optionally substituted with one or more halo or alkoxy,

R⁴ is hydrogen or phenyl,

15 R⁵ is hydrogen or phenyl,

m is 0, 1 or 2 and

n is 0, 1 or 2.

2. Process for preparing the hydroximic acid derivatives of the formula (I) and the salts thereof defined in claim 1

20 characterized in that

a) an aldoxim of the general formula (III) wherein R³, R⁴, R⁵, m and n are as defined in claim 1, is reacted in the presence of a base with an amine of the formula (IV/A) or (IV/B), wherein R¹ and R² are as defined in claim 1 and X is halo, or

- 20 -

b) an aldoxim of the general formula (III) wherein R³, R⁴, R⁵, m and n are as defined in claim 1, is reacted with epi-chlorohydrine and the aldoxim of the general formula (VI) thus obtained is reacted with an amine of the general formula (V) 5 wherein R¹ and R² are as defined above,

the aldoxim derivatives of the general formula (VII) obtained according to any of the processes a) or b) wherein R³, R⁴, R⁵, m and n are as defined above, after or without isolating, are reacted with inorganic acid chlorides or other 10 halogenating agents and the hydroximic acid halides of the general formula (VIII) thus obtained are hydrolyzed in an aqueous-alkaline medium, directly or through the ester derivatives, or

c) an aldoxim derivative of the general formula (II) wherein 15 the substituents are defined as above, is diazotized in the presence of NaNO₂ and HX wherein X is as defined above and the diazonium salt thus obtained, without or after isolation, is subjected to "boiling away" reaction.

and, if desired, the free bases obtained during the reaction 20 are transformed to the acid addition salt by reacting with organic or inorganic acids, or from the compounds obtained in the form of their salts the free bases are formed.

3. The process according to claim 2 characterized in that the reaction is carried out in a solvent.

25 4. The process according to claim 3 characterized in that as

- 21 -

solvent water, a mixture of water and an organic solvent or a mixture containing an aqueous and an organic solvent phase is used.

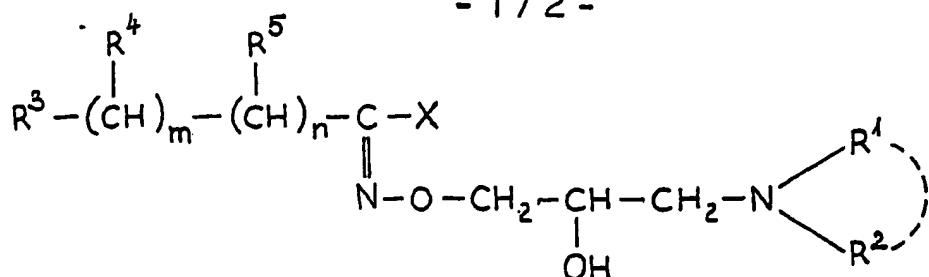
5. The process according to any of claims 2 to 4 characterized in that the reaction is carried out at a temperature of -10 to +140°C.

6. The compounds of the general formula (VIII) wherein R¹, R², R³, R⁴, R⁵, X, m and n are as defined in claim 1.

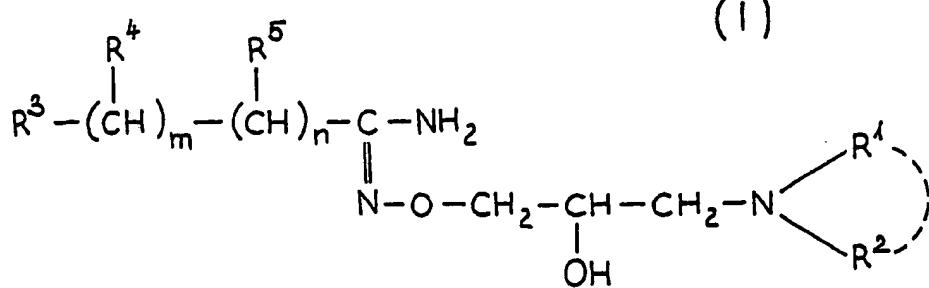
7. Pharmaceutical compositions preferably having special beta-blocking effect in case of diabetes, characterized by containing as active ingredient one or more of the compounds of the general formula (I).

8. The use of the compounds of the general formula (I) in the therapy of diabetes.

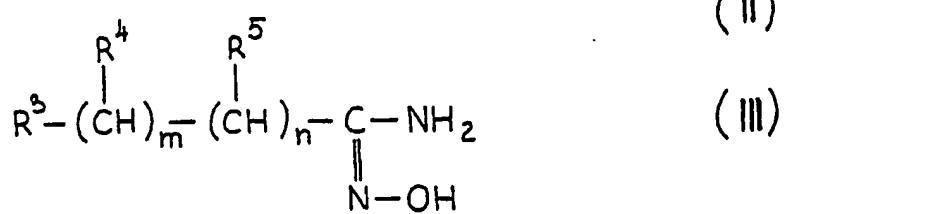
- 1 / 2 -



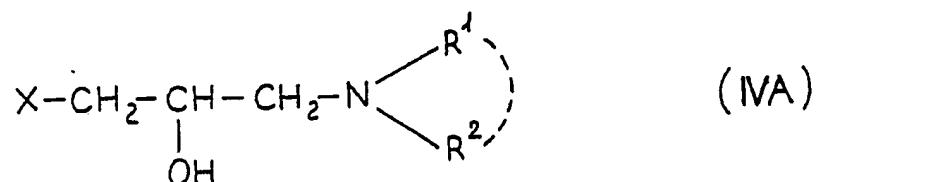
(I)



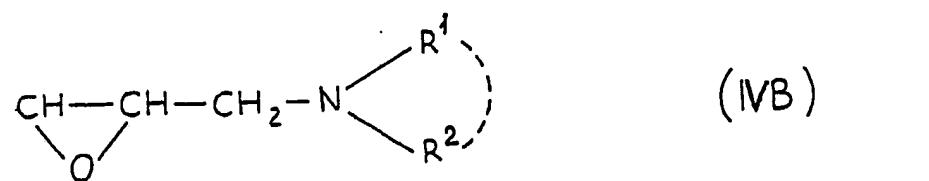
(II)



(III)



(IVA)

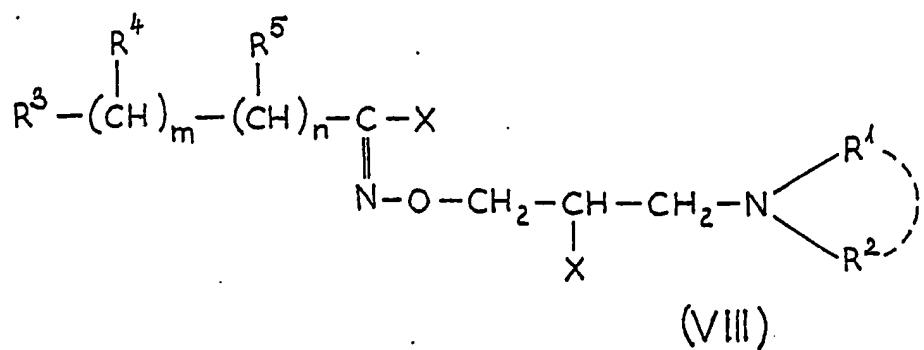
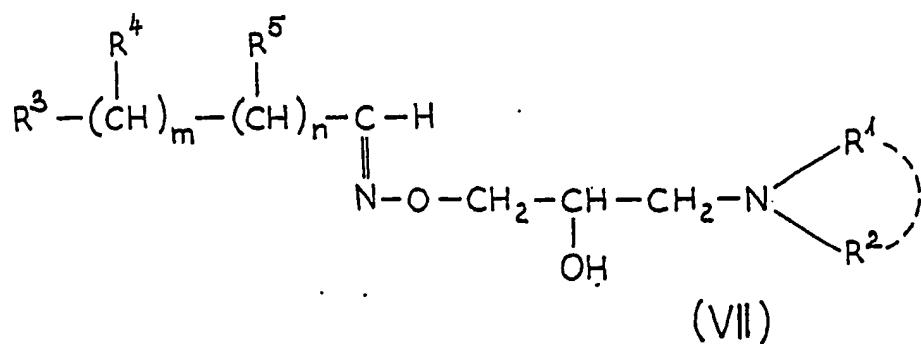
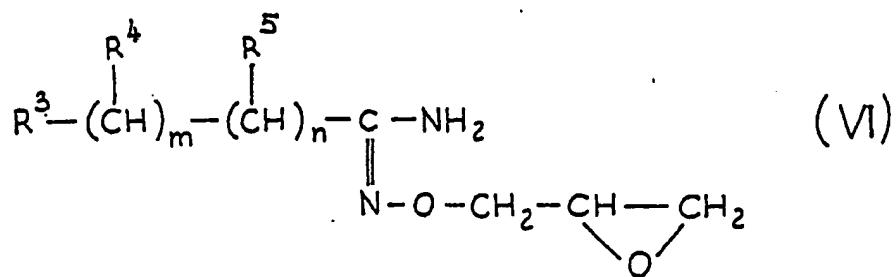


(IVB)



(V)

- 2 / 2 -



INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 89/00048

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁵: C 07 C 251/58, C 07 D 295/08, 295/12, C 07 C 249/12
A 61 K 31/15

II. FIELDS SEARCHED

Classification System	Classification Symbols	Minimum Documentation Searched *
		Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *
Int.Cl. ⁵	C 07 C 251/00, 249/00; C 07 D 295/00	

AT

III. DOCUMENTS CONSIDERED TO BE RELEVANT*

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. 13
A	US, A, 4 308 399 (KALMAN TAKACS et al.) 29 December 1981 (29.12.81), see columns 1-4.	(1-8)
A	AT, B, 355 554 (CHINOIN GYOGYSZER) 10 March 1980 (10.03.80), see claims 1-3; page 2, lines 1-45.	(1-8)

* Special categories of cited documents: *¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

*¹¹ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

*¹² document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

*¹³ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

*¹⁴ document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02 January 1990 (02.01.90)	02 January 1990 (02.01.90)
International Searching Authority AUSTRIAN PATENT OFFICE	Signature of Authorized Officer <i>[Signature]</i>

Anhang zum internatio-
nalen Recherchenbericht
Über die internationale
Patentanmeldung
Nr.

In diesem Anhang sind
die Mitglieder der
Patentfamilien der im
obengenannten interna-
tionalen Recherchenbe-
richt angeführten
Patentdokumente ange-
geben. Diese Angaben
dienen nur zur Unterrich-
tung und erfolgen ohne
Gewähr.

Annex to the International
Search Report on Interna-
tional Patent Application
No. PCT/HU 89/00048

This Annex lists the patent
family members relating to
the patent documents cited
in the above-mentioned Inter-
national search report. The
Austrian Patent Office is in
no way liable for these par-
ticulars which are merely
given for the purpose of in-
formation.

Annexe au rapport de
recherche internationale
relatif à la demande de
brevet international
n°.

La présente annexe indique
les membres de la famille de
brevets relatifs aux docu-
ments de brevets cités dans
le rapport de recherche inter-
nationale visé ci-dessus. Les
renseignements fournis sont
donnés à titre indicatif et
n'engagent pas la responsa-
bilité de l'Office autrichien
des brevets.

Im Recherchenbericht angeführtes Patent- dokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US-A - 4308399	29-12-81	None	
AT-B - 355554	10-03-80	AT-A - 8741/78 AT-B - 361457 AT-A - 6054/77 AU-B2- 521432 BE-A1- 858134 CA-A1- 1077506 CH-A - 630344 CS- P- 204008 CS- P- 204009 DD- C- 132433 DE-A1- 2738589 DK-A - 3797/77 DK-B - 150196 DK-C - 150196 ES-A5- 462346 ES-A1- 462346 FI-A - 772551 FI-B - 68396 FI-C - 68396 FR-A1- 2362845 FR-B1- 2362845 GB-A - 1582029 GR-A - 63623 HU- P- 177578 IL-AO- 52804 IL-A1- 52804 JP-A2-53050131 JP-B4-62016942 NO-A - 772958 NO-B - 144793 NO-C - 144793 PL- P- 106317 PL- P- 107628 SE-A - 7709482 SE-B - 435280 SE-C - 435280 SU- D- 730296 YU-A - 2023/77 YU-A - 2377/82	15-08-80 10-03-81 15-08-79 01-04-82 16-12-77 13-05-80 15-06-82 31-03-81 31-03-81 27-09-78 02-03-78 28-02-78 05-01-87 06-07-87 30-05-78 16-06-78 28-02-78 31-05-85 10-09-85 24-03-78 09-01-81 31-12-80 27-11-79 28-11-81 31-10-77 29-06-81 08-05-78 15-04-87 28-02-78 03-08-81 11-11-81 31-12-79 29-02-80 28-02-78 17-09-84 20-12-84 25-04-80 31-12-83 31-12-83

AT-B-355 554

10-03-80

AU-A1-28254/77	01-03-79
NL-A - 7709276	01-03-78
NZ-A - 188006	19-11-81
AR-A1- 223196	31-07-81
AR-A1- 227125	30-09-82
AR-A1- 228023	14-01-83
AR-A1- 231636	31-01-85
AT-A - 553978	15-04-81
AT-B - 364830	25-11-81
AT-A - 5659780	15-12-83
AT-A - 5660780	15-02-84
AT-B - 375350	25-07-84
AT-B - 375928	25-09-84
AU-A1-38478/78	07-02-80
AU-B2- 523324	22-07-82
CA-A1- 1109072	15-09-81
DD- C- 138318	24-10-79
DE-CO- 2861987	30-09-82
DK-A - 339578	02-02-79
EP-A1- 574	07-02-79
EP-B1- 574	04-08-82
ES-A1- 472208	16-03-79
FI-A - 782348	02-02-79
FI-B - 68231	30-04-85
FI-C - 68231	12-08-80
HU-B - 182938	28-03-84
IE-B - 47285	08-02-84
IL-AO- 55253	29-09-78
IL-A1- 55253	30-04-82
IT-A - 1156885	04-02-87
JP-A2-54027565	01-03-79
NO-A - 782615	02-02-79

NO-B - 150082	07-05-84
NO-C - 150082	15-08-84
PL- O- 208772	04-06-79
PL-B1- 117328	31-07-81
PL-B1- 117334	31-07-81
PL-B1- 117404	31-08-81
PT-A - 68365	01-07-78
US-A - 4323688	06-04-82
ZA-A - 7804323	25-07-79

DIALOG(R) File 351:Derwent WPI
(c) 2004 Thomson Derwent. All rts. reserv.

008276990

WPI Acc No: 1990-163991 /199021

XRAM Acc No: C94-103345

New O-3-amino-2-hydroxypropyl hydroxamic acid halide derivs. - used for treating diabetic angiopathy, with selective action on altered beta receptors

Patent Assignee: BIOREX KUTATO FEJLESZTO KFT (BIOR-N); BIOPHARM KUTATO & FEJLESZTOE KFT (BIOP-N); BIOREX KUTATO FEJLESZTOE KFT (BIOR-N); BIOREX KUTATO-FEJLESZTO KFT (BIOR-N); NAGY P L (NAGY-I); BIOREX KUTATO FEILESTE KFT (BIOR-N)

Inventor: ABRAHAM L; ALMASY A; BALAZS B; BLASKO G; BOROSS M; GACHALYI B; NAGY P L; NEMETH G; SZILBEREKY J; ZSILA G; ALMASI A; LITERATI NAGY P; NEMET G; SZILA G; LITERATI N P; BACHALYT B; BLASEO G; ZSILLA G; BALAAZS B

Number of Countries: 027 Number of Patents: 026

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 9004584	A	19900503				199021 B
PT 92041	A	19900430				199022
CA 2000830	A	19900420				199023
AU 8944186	A	19900514				199031
FI 9003075	A	19900619				199040
NO 9002703	A	19900903				199041
DK 9001497	A	19900619				199042
HU 54110	T	19910128				199109
EP 417210	A	19910320	EP 89911590	A	19891019	199112
ES 2020030	A	19910716	ES 893542	A	19891020	199133
JP 3502931	W	19910704	JP 89510821	A	19891019	199133
US 5147879	A	19920915	WO 89HU48	A	19891019	199240
			US 90499318	A	19900628	
HU 207988	B	19930728	HU 885405	A	19881020	199336
EP 417210	B1	19940309	EP 89911590	A	19891019	199410
			WO 89HU48	A	19891019	
US 5296606	A	19940322	WO 89HU48	A	19891019	199411 N
			US 90499318	A	19900628	
			US 92906402	A	19920701	
DE 68913737	E	19940414	DE 613737	A	19891019	199416
			EP 89911590	A	19891019	
			WO 89HU48	A	19891019	
IL 92000	A	19940624	IL 92000	A	19891016	199427
US 5328906	A	19940712	US 90499318	A	19900628	199427
			US 92906402	A	19920701	
			US 9372765	A	19930607	
FI 93214	B	19941130	WO 89HU48	A	19891019	199502
			FI 903075	A	19900619	
IE 65113	B	19951004	IE 893364	A	19891019	199547
NO 178148	B	19951023	WO 89HU48	A	19891019	199547
			NO 902703	A	19900618	
JP 96019078	B2	19960228	JP 89510821	A	19891019	199613
			WO 89HU48	A	19891019	
CA 2000830	C	19970916	CA 2000830	A	19891017	199750
RU 2093508	C1	19971020	SU 4830570	A	19891019	199824
			WO 89HU48	A	19891019	
PH 28843	A	19950405	PH 39379	A	19891018	199844
KR 154117	B1	19981201	WO 89HU48	A	19891019	200031

Priority Applications (No Type Date): HU 885405 A 19881020; WO 89HU48 A 19891019; JP 89510821 A 19891019; US 92906402 A 19920701

Cited Patents: AT 355554; US 4308399

Patent Details:

Patent No	Kind	Lan Pg	Main IPC	Filing Notes
-----------	------	--------	----------	--------------

WO 9004584 A

Designated States (National): AU DK FI JP KR NO SU US

Designated States (Regional): AT BE CH DE FR GB IT LU NL SE

EP 417210 A

Designated States (Regional): AT BE CH DE FR GB IT LI LU NL SE

US 5147879 A 6 A61K-031/445 Based on patent WO 9004584

HU 207988 B C07C-259/02 Previous Publ. patent HU 54110

EP 417210 B1 E 20 C07C-251/58 Based on patent WO 9004584

Designated States (Regional): AT BE CH DE FR GB IT LI LU NL SE

US 5296606 A 9 C07D-211/04 Div ex application WO 89HU48

Div ex application US 90499318

Div ex patent US 5147879

DE 68913737 E C07C-251/58 Based on patent EP 417210

Based on patent WO 9004584

IL 92000 A C07C-259/02

US 5328906 A 11 A61K-031/47 Div ex application US 90499318

CIP of application US 92906402

Div ex patent US 5147879

CIP of patent US 5296606

FI 93214 B C07D-295/088 Previous Publ. patent FI 9003075

IE 65113 B C07C-249/12

NO 178148 B C07D-295/088 Previous Publ. patent NO 9002703

JP 96019078 B2 10 C07C-259/02 Based on patent JP 3502931

Based on patent WO 9004584

CA 2000830 C C07C-257/02

RU 2093508 C1 11 C07C-251/58

PH 28843 A C07D-295/14

KR 154117 B1 C07C-251/58

Abstract (Basic): WO 9004584 A

Hydroxamic acid halides of formula (I) and their salts are new: In (I), X = F, Cl, Br or iodo; R1 = H or 1-5C alkyl; R2 = 1-5C alkyl, 5-7C cycloalkyl or phenyl (opt. subst. by OH), or NR1R2 is a 5-8 membered ring, opt. contg. an additional N and/or O atom and opt. fused to a benzene ring; R3 = H, phenyl, naphthyl or pyridyl, opt. subst. by 1 or more halo or alkoxy; R4 and R5 = H or phenyl; m and n = 0-2.

Also new are the intermediates of formula (VIII).

USE/ADVANTAGE - (I) are useful for treating diabetic angiopathy, esp. retinopathy and nephropathy. They have a selective beta-blocking action on receptors which has been altered as a result of diabetes but no significant effect on receptors in healthy blood vessels. (27pp Dwg.No.0/0)

Abstract (Equivalent): EP 417210 B

Hydroxamic acid derivatives of the general formula (I) and the salts thereof, wherein X is halo, such as fluoro, chloro, bromo and iodo, R1 is hydrogen or C1-5 alkyl, R2 is C1-5 alkyl, C5-7 cycloalkyl or phenyl optionally substituted with hydroxy, or R1 and R2, when taken together with the adjacent nitrogen, form a 5 to 8 membered ring optionally containing additional nitrogen and/or oxygen atom, which ring may also be condensed with a benzene ring, R2 is hydrogen, phenyl,

naphthyl or pyridyl optionally substituted with one or more halo or alkoxy, R4 is hydrogen or phenyl, R5 is hydrogen or phenyl, m is 0, 1 or 2 and n is 0, 1 or 2.

Dwg. 0/0

Abstract (Equivalent): US 5296606 A

Derivs. of O-(3-amino-2-hydroxypropyl)-hydroxamic acid halides of formula (VIII) are new. In the formula, X is halo; R1 and R2 together with attached N form 5- or 8-membered satd. ring; R3 is H, Ph, naphthyl, or pyridyl opt. substd. by one or more halo or alkoxy; R4 and R5 are H or Ph; m and n are 0-2.

USE - Treatment of diabetic angiopathy., These cpds. are special selective beta blockers which convert alpha adrenoreceptors which have been modulated into beta receptors by diabetes mellitus back into normal alpha adrenoreceptors, so correcting vascular deformations.

Applicable to all forms of diabetic micro- and macro-angiopathy, esp. diabetic retinopathy and nephropathy.

Dwg. 0/0

US 5147879 A

Hydroxamic acid derivs of formula R3-(CH(R4))^m-(CH(R5))ⁿ-C(X)=N-OCH₂-CHCOH)-CH₂-NR₁R₂ (I) and their salts are new, where X is F, Cl, Br or I; R1 is H or 1-5C alkyl; R2 is 1-5C alkyl or 5-7C cycloalkyl; or NR₁R₂ form a 5-8 membered satd. ring; R3 is H, phenyl, naphthyl, or pyridyl opt. substd. by one or more halo and/or alkoxy; R4 and R5 are independently H or Ph; m and n are independently 0-2.

USE/ADVANTAGE - The cpds. do not influence (or only slightly) the adrenergic reactions of healthy blood vessels, but show a strong effect on the adrenergic receptors deformed by diabetes mellitus. This effect appears as a selective beta-blocking effect, and (I) are useful for treating diabetic angiopathy, esp. diabetic retinopathy and diabetic nephropathy. They are ineffective on non-diabetic persons.

(Dwg. 0/0)

Title Terms: NEW; AMINO; HYDROXYPROPYL; HYDROXAMIC; ACID; HALIDE; DERIVATIVE; TREAT; DIABETES; SELECT; ACTION; ALTER; BETA; RECEPTOR

Derwent Class: B03; B05

International Patent Class (Main): A61K-031/47; C07C-249/12; C07C-251/58; C07C-257/02; C07C-259/02; C07D-211/04; C07D-295/088; C07D-295/14

International Patent Class (Additional): A61K-031/13; A61K-031/135; A61K-031/15; A61K-031/21; A61K-031/395; A61K-031/405; A61K-031/435; A61K-031/44; A61K-031/445; C07C-219/06; C07C-259/04; C07C-295/12; C07D-207/00; C07D-209/04; C07D-211/00; C07D-211/60; C07D-213/04; C07D-213/44; C07D-213/54; C07D-213/78; C07D-215/00; C07D-223/00; C07D-225/00; C07D-231/00; C07D-237/00; C07D-243/00; C07D-295/00; C07D-295/08; C07D-295/12; C07D-295/121; C07D-295/15; C07D-401/12; C07D-413/12; C07D-450/00; C07D-471/06

File Segment: CPI

Manual Codes (CPI/A-N): B07-H03; B10-A18; B12-E06B; B12-G03; B12-H05; B12-L04

Chemical Fragment Codes (M2):

01 D010 D011 D012 D019 D020 D029 D040 D049 D601 D632 F010 F011 F012 F013 F014 F019 F020 F021 F431 F433 F553 F653 G001 G002 G003 G010 G011 G012 G013 G015 G019 G020 G021 G022 G029 G030 G040 G050 G100 G111 G112 G113 G221 G553 G563 H102 H103 H141 H161 H181 H201 H4 H401 H402 H441 H461 H481 H482 H521 H541 H542 H601 H602 H603 H604 H621 H641 H8 K0 K8 K840 L3 L353 L640 M121 M122 M123 M129 M132 M135 M139 M150 M210 M211 M212 M213 M214 M215 M216 M220 M221 M222 M223 M224 M225 M226 M231 M232 M233 M263 M272 M273 M280 M281 M282 M311 M312 M313 M314 M315 M321 M322 M323 M331 M332 M333 M340 M342 M343 M344

M372 M373 M383 M391 M392 M412 M413 M414 M415 M416 M510 M511 M512
M520 M521 M522 M530 M531 M532 M533 M540 M541 M620 M640 M650 M710
M903 M904 P520 P816 9427-37701-N

Generic Compound Numbers: 9427-37701-N